
**Ophthalmic implants — Intraocular
lenses —**

Part 6:
Shelf-life and transport stability

Implants ophtalmiques — Lentilles intraoculaires —

Partie 6: Durée de conservation et stabilité pendant le transport

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 11979-6 was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

This second edition cancels and replaces the first edition (ISO 11979-6:2002) which has been technically revised.

ISO 11979 consists of the following parts, under the general title *Ophthalmic implants — Intraocular lenses*:

- *Part 1: Vocabulary*
- *Part 2: Optical properties and test methods*
- *Part 3: Mechanical properties and test methods*
- *Part 4: Labelling and information*
- *Part 5: Biocompatibility*
- *Part 6: Shelf-life and transport stability*
- *Part 7: Clinical investigations*
- *Part 8: Fundamental requirements*
- *Part 9: Multifocal intraocular lenses*
- *Part 10: Phakic intraocular lenses*

Introduction

The purpose of a stability study is to ascertain that the properties of a product, in this case an intraocular lens (IOL), remain within specified limits for a sufficiently long period of time under the influence of a variety of environmental conditions.

The storage stability of the intraocular lens material is an important factor in the overall investigation of a new lens material, a new combination of given lens materials, a new packaging material or a new manufacturing process. To assess this, a study of the ageing of the lenses in their containers is performed.

Changes in the composition and material, material suppliers, manufacturing conditions (including the sterilization process), or the package design or material could affect the shelf-life and could therefore necessitate renewed investigations. The need for studies of product stability, package integrity and transport stability can be assessed using ISO 14971.

The design of the stability tests should be based on the known properties of the material from which the intraocular lens is made, and the recommendations for use of the intraocular lens. Knowledge of the quantity and identity of extractable substances found after storage or accelerated ageing studies are of importance in evaluating new intraocular lens materials.

On the basis of the information obtained, transport and storage conditions can be recommended that will maintain the quality of the intraocular lens in relation to its safety, efficacy and acceptability, throughout the proposed shelf-life, i.e. during storage and distribution up until the moment of dispensing. The results obtained are also used to determine the expiration date.

In practical terms it is the stability of the material from which the intraocular lens is made that is being tested, along with the integrity of the packaging that maintains the necessary environment of the intraocular lens. Stability studies for intraocular lenses are thus material specific, i.e. this type of study need not be performed for more than one intraocular lens model for a given combination of IOL material(s), packaging materials and manufacturing processes.

Stability studies of intraocular lenses allow the determination of the shelf-life and package suitability as well as recommendations for transport and storage conditions.

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Ophthalmic implants — Intraocular lenses —

Part 6: Shelf-life and transport stability

1 Scope

This part of ISO 11979 specifies tests by which the shelf-life of sterile intraocular lenses (IOLs) in their final packaging can be determined. These tests include procedures to establish the stability of IOLs in distribution and storage.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11979-1, *Ophthalmic implants — Intraocular lenses — Part 1: Vocabulary*

ISO 10993-5, *Biological testing of medical devices — Tests for in vitro cytotoxicity*

ISO 10993-12, *Biological testing of medical devices — Sample preparation and reference materials*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO/TR 22979, *Ophthalmic implants — Intraocular lenses — Guidance on assessment of the need for clinical investigation of intraocular lens design modifications*

3 Terms and definitions

For the purposes of this document, the terms and definitions of ISO 11979-1 apply.

4 Requirements

4.1 General

If, following a risk analysis in accordance with ISO 14971, it is found that a product stability study, a package integrity study and/or a transport stability study are needed, this part of ISO 11979 shall apply to the planning and conduct of these studies.

A study protocol shall be developed prior to initiation of the study.

The study shall demonstrate that the parameters assessed with regard to performance, safety and product acceptability are within the original manufacturing specifications at the conclusion of the study.

In view of the fact that sufficiently long experience of storage of a new intraocular lens may not have been accumulated by the time it is brought to the market, the results of accelerated tests (see 4.3.2) are acceptable for initial labelling purposes, i.e. to establish a shelf-life to be used in the information on the product. A maximum of five years of shelf-life can be claimed by a real-time study or an accelerated study regardless of material used in the intraocular lens. An accelerated study shall however always be verified by a real-time study. The same product or a Level A modification of it (see ISO/TR 22979) shall be used in the real-time study. The real-time study shall be started before the release of the new intraocular lens to the market. The real-time study results always take precedence over the accelerated study results.

In case a manufacturer wishes to maintain the possibility of resterilizing finished intraocular lens lots, the finished intraocular lens lot(s) used in the stability study shall have undergone the maximum number of sterilization cycles allowed under the manufacturer's procedures.

4.2 Materials and methods

4.2.1 Test samples

The studies shall be performed using IOLs from finished intraocular lens lots (see ISO 11979-1). The proposed sample sizes are described in Annex A.

4.2.2 Methods

Suitable methods shall be chosen for any tests contained in the study protocol. The methods selected shall be recorded. Annex B contains suggested tests. Due to the variation in product and package materials and design, other tests could be more appropriate, e.g. for possible changes to the storage solution for IOLs stored in a solution. The methods selected shall be recorded and the details of validation for each test method, demonstrating the capability of the method, shall also be documented.

In certain cases more than one of the tests listed in Annex B can be performed on a single IOL (e.g. dioptric power, imaging quality and spectral transmission can all be measured on the same IOL), thereby reducing the total number of intraocular lenses required.

4.3 Product stability

4.3.1 General

If the risk analysis in accordance with ISO 14971 shows a need for a shelf-life study, the following shall apply. The rationale for choice of tests shall be documented in the risk management plan.

The shelf-life of an IOL shall be established based on data from at least three lots of finished IOLs (low, medium and high dioptric power ranges, each range comprising one or more dioptric powers), both for real-time studies and accelerated studies.

Based on a manufacturer's experience with the IOL material(s), packaging material(s), sterilization process and packaging process, a manufacturer's risk analysis can support the adequacy to perform a study on only one lot of product.

4.3.2 Real-time shelf-life study

4.3.2.1 Test parameters

The following parameters shall be considered for inclusion when a real-time shelf-life study is planned:

- a) dimensions;

- b) dioptric power;
- c) imaging quality;
- d) surgical manipulation;
- e) recovery of properties following simulated surgical manipulation (for foldable IOLs);
- f) surface and bulk homogeneity;
- g) compression force (samples from one or more dioptric power lots);
- h) dynamic fatigue (samples from one or more dioptric power lots);
- i) spectral transmission;
- j) exhaustive extraction (samples from one or more dioptric power lots);
- k) cytotoxicity (if an increase is seen in the content of extractables and/or if a new substance is present); it is sufficient to perform cytotoxicity testing on IOL samples from one dioptric power lot. In addition to testing of the IOL itself, an aqueous extract of the IOL also needs to be tested; both tests shall be performed in accordance with ISO 10993-5; for the aqueous extraction, the ratio of surface area to volume of extraction medium specified in ISO 10993-12 can be proportionally adjusted to accommodate the small size of the IOL;
- l) specific surface tests (if warranted).

References to suggested test methods are to be found in Annex B.

Testing for changes due to interaction with the packaging material shall also be considered, as shall testing for changes in surface treatments as well as the concentration of additives in the IOL or additives in a solution in which the IOL is stored.

An example of a calculation of the number of IOLs to be used in a shelf-life and transport stability study for an IOL made from a new material can be found in Annex A.

4.3.2.2 Study procedure

The following is the procedure for real-time stability studies. Intraocular lenses to be tested shall, if applicable, at each instance be evenly distributed among the different power groups.

- a) Assign a unique identification to each individual intraocular lens in the total sample and put that identification on the intraocular lens packaging.
- b) Collect the intraocular lenses to be tested initially and carry out the tests of the protocol. Record the unique identifications, the results and measurement conditions.
- c) Transfer the remaining packages to storage under controlled conditions at the recommended storage condition (e.g. temperature $25\text{ °C} \pm 2\text{ °C}$ and relative humidity $60\% \pm 20\%$). Record actual temperature, relative humidity and date.
- d) Monitor temperature and relative humidity, regularly during the course of the study in a manner such that fluctuations in temperature and relative humidity are also recorded.
- e) In accordance with the protocol, periodically remove a sufficient number of intraocular lenses for testing. Carry out the tests of the protocol. Record the unique identifications, the results and measurement conditions.

- f) Collect the intraocular lenses to be tested at the expiration date. Carry out the tests of the protocol. Record the unique identifications, the results and measurement conditions.

The parameters measured shall remain within the specified limits of the applicable parts of ISO 11979. In case there are no limits specified in ISO 11979, the parameters measured shall remain within the manufacturer's internal finished product release specifications. If a parameter is found to no longer conform, and this finding is confirmed by an investigation, then the maximum shelf-life is determined by the last conforming measurement point.

4.3.3 Accelerated shelf-life study

Studies under accelerated conditions are likely to speed up any degradation processes, and may therefore permit extrapolation of intervals under accelerated conditions to intervals at normal storage conditions. The same parameters as for real-time studies [4.3.2.1 a) to l)] shall be considered for inclusion when an accelerated shelf-life study is planned. References to suggested test methods can be found in Annex B. The same study procedures (except temperature and humidity) used for real-time studies [4.3.2.2 a) to f)] are also valid.

For microbial barrier testing, the accelerated conditions shall involve storage at a specified temperature and with a relative humidity of at least 40 %. If a manufacturer wishes to perform sterility testing in lieu of microbial barrier testing, the storage temperature shall be not more than 45 °C.

The real-time shelf-life is calculated by multiplying the studied time period by a factor of $2^{(T_a - T_0)/10}$, where T_a is the accelerated temperature and T_0 is the recommended storage temperature for the intraocular lens investigated.

It is important that intraocular lenses to be measured are allowed to equilibrate to the same conditions as at the initial measurements before being tested.

4.4 Package integrity

If the risk analysis in accordance with ISO 14971 shows that a package integrity study needs to be performed, the following shall apply. The rationale for choice of tests shall be documented in the risk management plan.

Packaging from three sterilization runs (containing or not containing IOLs) shall be used for the package integrity study.

Package integrity studies can also be performed as accelerated studies, using the same conditions and interpretations as shown under 4.3.3, with the proviso that a real-time study is started prior to putting the product on the market.

For a package integrity study, a minimum of the following tests shall be performed:

- a) legibility of labelling;
- b) seal/closure integrity;
- c) microbial barrier or whole package physical integrity.

References to suggested test methods are to be found in Annex B. Until an internationally accepted standard for microbial barrier testing is established, the method used can be evaluated in accordance with ISO 11607-1.

4.5 Transport stability

If the risk analysis in accordance with ISO 14971 shows a need for a transport stability study, the following shall be considered. The rationale for choice of tests shall be documented in the risk management plan.

The complete, filled intraocular lens packages (in their normal transport package) shall be able to withstand extremes of the temperature and humidity (as expected in shipping), vibration and being dropped. Both the

packaging and the product shall be inspected following completion of the pre-test conditioning. The IOL shall be considered to have satisfactorily passed the test if the IOL is free from physical damage when visually inspected under magnification. The packaging must also continue to provide functional protection to the IOL.

A minimum of the following tests shall be performed:

- a) legibility of labelling (empty packages can be used);
- b) surface and bulk homogeneity of the IOL (sealed packages shall be used);
- c) seal/closure integrity (empty packages can be used);
- d) microbial barrier or whole package physical integrity (empty packages can be used).

References to suggested test methods can be found in Annex B.

For transport stability studies where complete packages with IOLs are needed, it is adequate to use only one intraocular lens lot of the medium dioptric power for all tests.

4.6 Results

A report comprising the following information shall be kept on file:

- a) summary of the results;
- b) copy of the labelling of the intraocular lens;
- c) manufacturing lot numbers, lot sizes, dates of manufacture and name of the manufacturer of the intraocular lens;
- d) details of the packaging, including the materials used and descriptions of the container and the closure;
- e) description of conceivable changes of the product, the materials used and the product's mechanical and optical properties;
- f) interpretation of the results in terms of shelf-life, storage and shipping recommendations;
- g) name of the test laboratory, dates of testing and an approval signature.

For each finished intraocular lens lot the initial results, the results during storage and at the end of the proposed shelf-life shall be presented in tabular form for easy interpretation.

5 Test methods and sampling

Suggested test methods are referenced in Annex B.

Unless the method description specifies the sample size, a minimum of 10 intraocular lenses shall be used for each test at every testing occasion.

Annex A (informative)

Shelf-life study example

A.1 Assumptions

A manufacturer has a foldable IOL made from a new material (without any surface modification) that will undergo shelf-life testing. The IOL is packaged in a new container. Since the manufacturer wants to allow one resterilization, all test samples undergo two sterilization cycles at the beginning of the shelf-life study. The manufacturer wants to ultimately validate a five year shelf-life but intends to enter the market with a one year shelf-life and then increase that expiration dating by one year at a time as the data supporting the shelf-life dating becomes available.

The manufacturer intends to perform an accelerated shelf-life study and therefore includes three lots to be tested under accelerated conditions and three lots that are stored under real-time conditions to validate the acceleration conditions for the test material.

A.2 Sample requirements

A.2.1 General

There are five evaluation time points for the test samples (1, 2, 3, 4 and 5 years).

The power range of the manufacturer's IOL is 6 D to 30 D. The manufacturer makes the following designations:

low dioptric power:	6 D
medium dioptric power:	18 D
high dioptric power:	30 D

Three finished intraocular lens lots are needed at each of the time points for both real-time and accelerated product stability testing (one lot of low dioptric power, one of medium dioptric power, one of high dioptric power).

Three sterilization runs are evaluated at each of the time points for both real-time and accelerated package integrity testing.

One lot of IOLs is evaluated once for transport stability testing (of medium dioptric power). Some of the units for transport stability testing can be complete packages without IOLs.

A single sample of an IOL can be used in more than one test in the evaluation of product stability.

A.2.2 Product stability and package integrity testing (for each time point)

A.2.2.1 Product stability

- thirty packages, with IOL: ten each of low, medium and high dioptric power, for imaging quality, spectral transmittance, dimensions, surface and bulk homogeneity, and surgical manipulation tests;

- b) ten packages, with medium dioptric power IOL, for compression force;
- c) ten packages, with medium dioptric power IOL, for dynamic fatigue;
- d) thirty packages, with IOL: ten each of low, medium and high dioptric power, for recovery of properties following simulated surgical manipulation;
- e) ten packages, with medium dioptric power IOL, for exhaustive extraction testing;
- f) thirty packages, with medium dioptric power IOL, for cytotoxicity tests (if, as in this example, an increase in the content of extractables was seen together with a new substance in the extract).

A.2.2.2 Package integrity

- a) thirty packages (ten per sterilization run), with or without IOL, for microbial barrier or whole package physical integrity tests;
- b) thirty packages (ten per sterilization run), with or without IOL, for legibility of labelling and seal integrity tests.

A.2.3 Transport stability (tested only once)

Based on how the IOLs are expected to be transported, the manufacturer determines the worst case environmental conditioning and handling necessary.

A total of sixty samples (twenty packages with IOL and forty with or without IOL) need to be conditioned and evaluated at one time point:

- a) twenty packages, with any dioptric power IOL, for assessment of physical damage and surface and bulk homogeneity of the IOL;
- b) thirty packages, with or without IOL, for microbial barrier or whole package physical integrity tests;
- c) ten packages, with or without IOL, for legibility of labelling and seal/closure integrity tests.

A.3 Total sample size

In this example the manufacturer has chosen to perform the cytotoxicity test. As can be seen from Table A.1, the accelerated test programme then requires 600 packages with IOLs and 300 packages with or without IOLs. Another 600 packages with IOLs and 300 packages with or without IOLs will be required for the subsequent real-time test programme. The transport stability testing (Table A.2) requires twenty packages with IOLs and forty packages with or without IOLs. Therefore, a total of 1 220 packages with IOLs and 640 packages with or without IOLs are needed for all the necessary studies.

A.4 Results

The manufacturer performs the study under accelerated conditions and when testing at the one-year time period no failures are observed. The IOL is then labelled for a one-year shelf-life. At the simulated two-year time point, there are also no failures and the shelf-life is extended to two years. At the simulated three-year time point, a seal integrity failure of the test samples is observed and confirmed by an investigation. Therefore the final shelf-life is two years.

The manufacturer uses the results of the real-time testing to confirm the study results of the accelerated study. If the real-time study is continued beyond two years and there are no failures in coming years, the shelf-life can be extended based on the real-time results.

Table A.1 — Real-time or accelerated shelf-life study of IOL and packaging
(number of IOLs and packages needed)

Study	Test	Example text ref.	Dioptric power and year ^a																
			Low dioptric power					Medium dioptric power					High dioptric power						
			1	2	3	4	5	1	2	3	4	5	1	2	3	4	5		
Product stability	Dioptric power	A.2.2.1, a)																	
	Imaging quality																		
	Spectral transmittance		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Dimensions																		
	Surface bulk																		
	Surgical manipulation																		
	Compression force	A.2.2.1, b)	—	—	—	—	—	10	10	10	10	10	—	—	—	—	—	—	
	Dynamic fatigue	A.2.2.1, c)	—	—	—	—	—	10	10	10	10	10	—	—	—	—	—	—	
	Recovery properties	A.2.2.1, d)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	Exhaustive extraction	A.2.2.1, e)	—	—	—	—	—	10	10	10	10	10	—	—	—	—	—	—	
Cytotoxicity	A.2.2.1, f)	—	—	—	—	—	30	30	30	30	30	—	—	—	—	—	—		
Total packages with IOL per study: 600			20	20	20	20	20	80	80	80	80	80	20	20	20	20	20		
Package integrity ^b	Legibility label	A.2.2.2, b)	—	—	—	—	—	30*	30*	30*	30*	30*	—	—	—	—	—		
	Seal/closure		—	—	—	—	—	30*	30*	30*	30*	30*	—	—	—	—	—		
	Microbial barrier	A.2.2.2, a)	—	—	—	—	—	30*	30*	30*	30*	30*	—	—	—	—	—		
Total packages with or without IOL: 300			—	—	—	—	—	60*	60*	60*	60*	60*	—	—	—	—	—		
^a Numbers with asterisks indicate packages that can be with or without IOL. ^b The thirty samples represent ten samples each from three sterilization lots.																			

Table A.2 — Transport stability testing of IOL and packaging
(number of IOLs and packages needed)

Pre-test conditioning	Tests on IOLs	Tests on packaging (with or without IOLs)
Selected temperatures and humidity(ies) Vibration test Drop test	Physical damage assessment Surface and bulk homogeneity Twenty samples needed [see A.2.3 a)]	Microbial barrier or whole package physical integrity Thirty samples needed [see A.2.3, b)] Label legibility Seal/closure integrity Ten samples needed [see A.2.3, c)]
Total packages with IOL: twenty samples		
Total packages with or without IOL: forty samples		